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20582	7590	07/22/2005	EXAMINER	
JONES DAY			LAMBERTSON, DAVID A	
51 Louisiana Aveue, N.W			ART UNIT	
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1636

DATE MAILED: 07/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/608,078

Applicant(s)

PAN ET AL

Examiner

David A. Lambertson

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 02 May 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-16 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-14 is/are rejected.
- 7) ☒ Claim(s) 15 and 16 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☒ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I (claims 2 and 11 as they relate to the use of a promoter that is responsive to acetic acid, including linking claims 1, 3-10 and 12-16) in the reply filed on May 2, 2005 is acknowledged. The traversal is on the ground(s) that a single search directed to a promoter that is inducible by an organic acid would be sufficient to search the complete scope of the invention, and would not impose a serious burden on the Office. This is not found persuasive because the previous restriction requirement established that each promoter contained in the Markush-type group of claims 2 and 11 were structurally and functionally distinct inventions, each of which required a separate search. Although each of these specific inventions is encompassed by a general concept, a search of the general concept would be burdensome in the context of the individual promoters, should the general concept itself not be allowable; this is because separate and burdensome searches would be required for each of the individual groups set forth in the restriction requirement, pending the non-allowability of the general concept. As such, "linking claim practice" was properly employed, indicating that if the general concept were to be found allowable, the individual inventions encompassed by the general concept would be rejoined. However, as set forth below, the general concept was not found to be allowable, thus a search burden for each of the individual groups persisted, and the restriction requirement is proper.

The requirement is still deemed proper and is therefore made FINAL.

Claims 1-16 are pending and under examination in the instant application with regard to a promoter that is responsive to acetic acid.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in The Republic of Korea on September 5, 2000. It is noted, however, that applicant has not filed a certified copy of the 00-52464 application as required by 35 U.S.C. 119(b) in either the parent application (09/946,376, now Abandoned) or the instant application.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

The Oath is illegible. A new copy is required.

Specification

A substitute specification without the claims is required pursuant to 37 CFR 1.125(a) because the application is replete with statements that do not conform to proper English vernacular. For example, on page 2, lines 23-26, the statement "Therefore, the object of the present invention is to provide a new method of protein synthesis by means of a protein expression system which is characterized in that the system contains a promoter which has a transcriptional activity during the resting stage of cell culture and also a protein expression is

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regulated with ease as well as efficiency” does not conform to proper English grammar. The specification contains numerous similar digressions.

A substitute specification filed under 37 CFR 1.125(a) must only contain subject matter from the original specification and any previously entered amendment under 37 CFR 1.121. If the substitute specification contains additional subject matter not of record, the substitute specification must be filed under 37 CFR 1.125(b) and must be accompanied by: 1) a statement that the substitute specification contains no new matter; and 2) a marked-up copy showing the amendments to be made via the substitute specification relative to the specification at the time the substitute specification is filed.

The disclosure is additionally objected to because of the following informalities: the Brief Description of the Figures lacks a reference to multiple panels in the first sentence for the description of Figures 2, 5 and 7. When figures contain multiple panels, this should be indicated in the first line of the description for each figure.

Appropriate correction is required.

Claim Objections

Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Specifically, the claim broadens the scope of the dependent claim by including promoters from other bacteria, as well as from eukaryotes.

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Claims 15 and 16 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claim. See MPEP § 608.01(n). Accordingly, claims 15 and 16 have not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant claims a method of producing a desired protein using cells comprising a vector comprising *any* promoter that can be induced by *any* organic acid compound. The claims read on a broad genus of promoters and organic acids that can be used to induce the expression of a protein.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics sufficient to show applicants were in possession of the claimed genus. In the instant case, the specification does not

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sufficiently describe a representative number of species by actual reduction to practice or by disclosure of relevant identifying characteristics.

Applicant claims the promoters (and their ability to be induced by multiple organic acids) by function only, without any disclosed or known correlation between the elements and their function. The specification only provides teachings using the *acs* promoter as obtained from *E. coli*, and its induction by acetic acid and succinic acid. The specification does not teach how to envision other promoters that are inducible by organic acids by identifying specific structural or functional characteristics that are relevant to the induction process. Furthermore, the instant specification does not identify additional promoters that can be induced by organic acids. Finally, the specification does not teach that all organic acids can function to induce the promoter activity of the specific promoter that is claimed. As a result, the skilled artisan cannot envision a sufficient number of embodiments of the instant invention from the instant specification because the specification only discloses a single promoter without further disclosing the specific relevant structural/functional requirements of the promoter that confer inducibility by organic acids.

The prior art does not provide sufficient information on the subject to overcome the written description requirements. There is no description in the prior art that allows one to envision a representative number of organic acid inducible promoters by disclosing structural or functional features of these hotspots so that one of skill in the art could identify and use said sequences in the instant invention. It is unclear from the prior art what other promoters can be induced by organic acids because it is unclear what actually makes a particular sequence inducible by organic acids. Finally, it is unclear that all organic acids are capable of inducing expression from the single promoter that is described in the instant specification. Thus the

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skilled artisan cannot rely on the prior art to envision a sufficient number of embodiments of the instant invention to see that the applicant was in possession of the claimed genus.

Neither the specification of the instant application or the prior art teaches a structure-function relationship for a representative number of organic inducible promoters. As a result, the skilled artisan would not be able to envision the claimed invention by relying on the teachings of the prior art or the instant specification. Therefore applicant has not satisfied the written description requirement to show the skilled artisan that they were in possession of the claimed genus.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is rejected under 35 U.S.C. 112, second paragraph, because the claim recites the limitation "producing a desired protein by gene recombination", but there does not appear to be a step corresponding to gene recombination in the claim. Furthermore, there does not appear to be any reliance on gene recombination in the method as disclosed in the specification. Thus, the term is indefinite because it is unclear what the term encompasses.

Claim 3 is missing the article "the" in two locations, specifically after "said promoter includes" in the first line and before "acs gene" in the second line.

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Claim 4 recites the limitation "said *acs* promoter" in the first line of the claim. There is insufficient antecedent basis for this limitation in the claim. Claim 3, from which claim 4 depends, mentions a promoter and mentions an *acs* gene, but does not specifically mention an *acs* promoter.

Claim 4 is rejected under 35 U.S.C. 112, second paragraph, because the claim recites the language that the "...promoter is derived from...", however, it is unclear if the promoter is modified in some way to be a promoter, or if the promoter is simply obtained from the sources listed. Changing "derived" to "obtained" would be remedial.

Claims 4 and 13 are dependent on claims 3 and 12, which refer to an *E. coli* promoter region. However, claims 4 and 12 refer to eukaryotic organisms such as yeast, and it is unclear how a yeast promoter can be obtained from a bacterial promoter. Changing the dependency of claims 4 and 12 would be remedial.

Claims 5, 6, 8 and 14 recite improper Markush language, using multiple conjunctions. Proper Markush terminology recites only a single 'and' conjunction following the penultimate member of the group. Use of 'or' is improper because it renders the claim language indefinite because it is unclear what the members of the group actually are.

Claims 5, 11 and 14 are improper Markush groups because they contain improper Markush language. Specifically, the claims recite the phrase "any one selected from the group consisting of...", but it is unclear what "one" refers to. Removal of the "any one" from the claims followed by any necessary grammatical corrections would be remedial.

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Claims 5, 6 and 14 recite the phrase "said gene contains a DNA fragment." The claim is indefinite because it is unclear if the gene is a chimera comprised of itself and a heterologous DNA fragment from another gene, or if the gene is itself the DNA fragment.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following rejections are predicated on the following interpretations of the claims.

First, the term "desired protein" is considered to mean any protein, as any given protein can be considered desirable to any given person. Second, the term "recovering the desired protein" is considered broadly to mean any separation of the protein from the environment in which it is produced (such as a cell lysis procedure). Finally, the term "producing a desired protein by gene recombination" is interpreted to mean "the recombinant production of a desired protein."

Claims 1-5 and 7-14 are rejected under 35 U.S.C. 102(b) as being anticipated by Shin *et al.* (*FEMS Microbiology Letters* **146**: 103-108, 1997; see entire document; henceforth Shin).

Shin teaches an expression vector using a 1.3 kb fragment containing the *acs* promoter from *E. coli* (see for example page 105, Figure 1) cloned into plasmid pKK233-8 to drive the expression of a desired protein, a functional CAT (chloramphenicol transferase) enzyme (see for example page 104, section 2.2). Shin also teaches that expression from this promoter was inducible in the presence of acetic acid, and that expression occurred during the stationary phase

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of cell growth (i.e., during the resting phase) as indicated by the need for a stationary phase-specific transcription factor (see for example page 105, left side). Thus, Shin teaches a vector comprising a bacterially derived promoter that is sensitive to induction by an organic acid during the resting stage of cellular growth, wherein the promoter comprises 1 kb of upstream DNA sequence that is operably linked to a gene of interest encoding a desired protein.

Shin further teaches the induction of this promoter in *E. coli* cells (a Gram-negative bacteria), and thus the production of a desired protein. The production of CAT is then measured by an enzymatic assay (see for example Fig, 2B-C). In order to perform a CAT activity assay, one must first extract the enzyme from the cells in which it is expressed, and react the enzyme with chloramphenicol. Thus, Shin necessarily teaches the recovery of a protein of interest in the broadest reasonable interpretation of the term.

Finally, Shin teaches inducing the expression of the protein of interest using minimal media, specifically including M9 minimal medium containing acetic acid without glucose (i.e., where acetic acid serves as the sole carbon source) (see for example page 104, section 2.1).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1-5, 7-14 and 6* are rejected under 35 U.S.C. 103(a) as being unpatentable over Shin in view of separate teachings in the instant specification.

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Shin teaches all of the elements set forth above in the rejection of claims 1-5 and 7-14 under 35 USC 102(b). Specifically, Shin teaches the expression and recovery of the enzyme CAT as a reporter for measuring expression from the *E. coli acs* promoter. However, Shin does not teach the recovery of a polypeptide such as *lacZ* (β -galactosidase). Shin does however teach the use of *lacZ* as a reporter protein in the reference (see for example section 2.1 on page 104), and it was well known in the art at the time of filing that different reporter proteins are interchangeable.

It would have been obvious for the ordinary skilled artisan to substitute the *lacZ* gene for the CAT gene in the methods taught by Shin because both genes can be used as reporters and are virtually interchangeable. The ordinary skilled artisan would have been motivated to switch the *lacZ* reporter gene with the CAT reporter gene in order to perform a valuable scientific control ensuring that the observed effects on the *acs* reporter were indeed a direct effect, and not simply an indirect effect of the growth conditions on CAT expression, stability or enzymatic activity (for example, to ensure that a medium component did not contain a co-activator substance that enhanced the activity of CAT). Absent evidence to the contrary and the skilled artisan would have had a reasonable expectation of success in practicing the claimed invention because the skilled artisan would recognize the interchangeability of different reporter proteins, given the common practice of doing so in the art.

Allowable Subject Matter

No claims are allowable.


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Any inquiry concerning this communication or earlier communications from the examiner should be directed to David A. Lambertson whose telephone number is (571) 272-0771. The examiner can normally be reached on 6:30am to 4pm, Mon.-Fri., first Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David A. Lambertson, Ph.D.
AU 1636



JAMES KETTER
PRIMARY EXAMINER